REMARKS

The presently claimed invention features probes that recognize certain variant sequences within the MTHFR gene and methods for using such probes.

On October 19, 2001 Applicants filed a Sequence Listing containing a nucleotide sequence of the MTHFR gene and several other genes, all of which were identified by name and GenBank® Accession Number in Table 10 of the present application. The Sequence Listing was used to amend the application to include the actual nucleotide sequences of the genes identified by name and GenBank® Accession Number in Table 10 of the application. The Sequence Listing was accompanied by a Declaration Regarding Incorporation by Reference. This declaration, signed by Vincent P. Stanton, Jr., stated that the sequences in the Sequence Listing were identical to those incorporated by reference in the application by inclusion of the GenBank® Accession Numbers in Table 10.

It has recently come to Applicants' attention that at least the sequence of the MTHFR gene in the October 19, 2001 Sequence Listing is not correct. Accordingly, Applicants have today submitted (sent to Box Sequence, U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA, 22202; a paper copy is enclosed herewith) a replacement sequence listing containing the correct MTHFR nucleotide sequence.[1] Also enclosed is a Declaration Regarding Incorporation by Reference signed by Vincent P. Stanton, Jr. This declaration states that:

> Applicant hereby declares that the Sequence Listing appended hereto consists of the same sequence information incorporated by reference in the above-referenced application by reference to the GenBank® Accession Number U09806.
>
> The sequence of SEQ ID NO:1 in the appended Sequence Listing is the same as that associated with GenBank® Accession number U09806 on July 20, 1998, the filing date of U.S. Serial No. 60/093,484, from which the present application claims priority. This particular version of GenBank® Accession No. U09806 is assigned the version identifier GI:945022. Exhibit A attached hereto is a printout from the GenBank® Database of GenBank® Accession No. U09806 [GI: 945022]. This printout shows that GenBank® Accession No. U09806 [GI: 945022] replaced an earlier version of the sequence GenBank® Accession No. U09806 [GI:499223] on August 17, 1995. Exhibit B is a printout from the

[1] The sequences of the other genes identified in Table 10 are not included in the sequence listing because the pending claims concern only the MTHFR sequence.

GenBank® Database of GenBank® Accession No. U09806 [GI:6174884] showing that it replaced GenBank® Database of Accession No. U09806 [GI:945022] on November 2, 1999.

In my Declaration regarding Incorporation By Reference filed on October 22, 2001 I mistakenly stated that the sequences in the Sequence Listing appended thereto were those incorporated by reference to GenBank® Accession numbers in the above-referenced application. However, for GenBank® Accession number U09806, the Sequence Listing appended to my October 22, 201 Declaration Regarding Incorporation by Reference had the incorrect version of GenBank® Accession number U09806, namely, GenBank® Accession number U09806 [GI:6174884] rather than GenBank® Accession number U09806 [GI:945022]. This error was made without deceptive intent.

Applicants recognize that the previously pending claims have been allowed. However, Applicants request that the Examiner examine the pending claims based on the corrected MTHFR nucleotide sequence in the Sequence Listing submitted herewith.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a $370.00 check for the Request for Continued Examination fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 13 NOV 2002

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Version with markings to show changes made

In the specification:

Table 10 beginning at page 171 has been amended as follows:

Table 10

Variance Table

Hugo	GID Variance Start	OMIM ID Variance	VGX Symbol	Description
U73338	U73338	156570	GEN-69	Methionine Synthase [(SEQ ID NO:1)]
	194	(-201)C>G		5'
	284	(-111)C>T		5'
	1136	742G>A		V248M
	1252	858C>T		Silent
	1334	940G>A		D314N
	1699	1305T>C		Silent
	3150	2756A>G		D919G
	3207	2813G>T		S938I
	3209	2815G>C		G939R
	5444	5050C>A		3'
	5551	5157G>A		3'
	5573	5179C>T		3'
	5659	5265T>C		3'
	5678	5284T>C		3'
	5874	5480C>T		3'
	5934	5540A>G		3'
D78586	D78586	114010	GEN-BR	CAD PROTEIN [(SEQ ID NO:2)]
	3434	3408C>T		Silent
	4313	4287T>C		Silent
	4799	4773A>G		Silent
	5255	5229C>T		Silent
	5455	5429G>A		R1810Q
	5507	5481T>C		Silent
	5810	5784C>T		Silent
	6128	6102C>T		Silent
	6626	6600C>T		Silent
	6686	6660C>T		Silent
U09178	U09178	274270	GEN-HA	Dihydropyrimidine Dehydrogenase [(SEQ ID NO:3)]
	166	85T>C		C29R

577	496A>G	M166V	
638	557A>G	Y186C	
1708	1627A>G	I543V	
3432	3351T>C	3'	
3682	3601C>T	3'	
3730	3649G>A	3'	
3925	3844A>G	3'	
3937	3856T>C	3'	

U19720 U19720 600424 GEN-I1 Folate Transporter (SLC19A1) [(SEQ ID NO:4)]

175	80G>A	R27H
341	246C>G	Silent
791	696C>T	Silent
1067	972G>A	Silent
1337	1242C>A	Silent
1997	1902T>C	3'
2100	2005^2006insG	3'
2582	2487T>G	3'
2617	2522C>T	3'
2652	2557T>C	3'

U92868 U92868 600424 GEN-LUK Homo sapiens reduced folate carrier (RFC1) gene, exons 1a, 1c and 1b [(SEQ ID NO:5)]

431	431A>G	Intron
441	441A>G	Intron
498	498C>T	Intron
579	579G>C	Intron
599	599G>C	Intron

X02308 X02308 188350 GEN-KL Thymidylate synthetase [(SEQ ID NO:6)]

1066	961T>C	3'
1136	1031A>G	3'
1497	1392T>A	3'

D00517 D00517 188350 GEN-LUC Thymidylate synthase, promoter [(SEQ ID NO:7)]

276	276C>T	Intron
321	321T>C	Intron
452	452G>A	Intron
457	457^insC	Intron
491	491C>A	Intron
533	533T>C	Intron
624	624A>C	Intron
639	639A>G	Intron
655	655T>C	Intron

D00596 D00596 188350 GEN-LUD Homo sapiens gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7, complete cds [(SEQ ID NO:8)]

701	701A>C	Intron
716	716A>G	Intron
732	732T>C	Intron
1293	1293A>G	Intron
1322	1322C>G	Intron
1379	1379T>C	Intron
1590	1590C>T	Intron
1688	1688C>G	Intron
2401	2401A>G	Intron
2429	2429G>A	Intron
2488	2488C>T	Intron
2594	2594G>T	Intron
2618	2618G>A	Intron
3083	3083G>A	Intron
3125	3125G>A	Intron
3212	3212C>T	Intron
3619	3619T>A	Intron
3635	3635G>A	Intron
4256	4256G>A	Intron
4898	4898A>G	Intron
5006	5006C>T	Intron
5062	5062G>A	Intron
5167	5167G>A	Intron
11069	11069A>G	Intron
11238	11238C>T	Intron
11293	11293T>G	Intron
11422	11422T>C	Intron
11686	11686C>T	Intron
12598	12598T>C	Intron
13171	13171T>C	Intron
13298	13298G>A	Intron
13645	13645T>C	Intron
13751	13751C>A	Intron
13782	13782T>C	Intron
13806	13806T>C	Intron
13813	13813T>C	Intron
14479	14479A>G	Intron
14546	14546^insT	Intron
14585	14585C>T	Intron
14729	14729G>A	Intron
14787	14787C>T	Intron
14795	14795G>A	Intron

	15041	15041T>C	Intron
	15343	15343G>A	Intron
	15449	15449G>A	Intron
	15502	15502G>A	Intron
	15545	15545C>T	Intron
	15589	15589A>G	Intron
	15769	15769C>T	3'
	15839	15839A>G	3'
	16148	16148G>A	3'
	16198	16198T>G	3'
	16202	16202G>T	Intron

X59618 X59618 180390 GEN-M3 Ribonucleotide reductase M2 polypeptide [(SEQ ID NO:9)]

	128	(-67)G>A	5'
	189	(-6)T>G	5'
	524	330C>G	Silent
	1399	1205T>A	3'
	1464	1270G>A	3'
	1636	1442C>T	3'
	1738	1544C>T	3'
	2259	2065T>C	3'

S72487 S72487 131222 GEN-3LD Thymidine phosphorylase, partial [(SEQ ID NO:10)]

	183	19G>A	D7N
	483	319C>T	3'
	601	437G>C	3'
	1299	1135G>A	3'

M58602 M58602 131222 GEN-LUB Thymidine phosphorylase, promoter and genomic [(SEQ ID NO:11)]

	124	124C>T	3'
	439	439G>A	3'
	1044	1044^insCT	3'
	1331	1331G>A	3'
	1977	1977G>A	Intron
	2149	2149G>A	Intron
	2467	2467A>G	Intron
	2634	2634C>G	Intron
	2975	2975G>A	Intron
	3116	3116G>T	Intron
	3255	3255A>C	Intron
	3344	3344T>C	Intron
	4051	4051C>A	Intron
	4782	4782G>A	Intron
	5022	5022T>C	Intron
	5266	5266G>A	Intron

	5285	5285C>G	Intron	
	5438	5438T>A	Intron	
	5482	5482C>T	Intron	
	5629	5629G>A	Intron	
	5648	5648C>T	Intron	
	5731	5731G>A	Intron	
M98045	M98045	136510	GEN-4C3	Homo sapiens folylpolyglutamate synthetase mRNA, complete cds [(SEQ ID NO:12)]
	802	732C>T	Silent	
	1747	1677G>T	3'	
	1900	1830T>C	3'	
U24253	U24253	136510	GEN-LUE	Human folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and partial cds [(SEQ ID NO:13)]
	1424	1424C>A	Intron	
	1649	1649G>A	Intron	
	2554	2554A>G	Intron	
U24252	U24252	136510	GEN-LUF	Folylpolyglutamate synthetase, promoter and exons 1-4 [(SEQ ID NO:14)]
	263	263A>G	Intron	
	266	266G>T	Intron	
	527	527C>G	Intron	
	1037	1037A>G	5'	
	1139	1139G>A	Intron	
	1217	1217C>T	Intron	
	1647	1647C>T	Intron	
	1955	1955G>A	Intron	
	2017	2017G>A	Intron	
	2037	2037G>A	Intron	
	2189	2189A>G	Intron	
	2282	2282C>T	Intron	
	2309	2309A>G	Intron	
U09806	U09806	236250	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds [(SEQ ID NO:15)] (SEQ ID NO:1)
	120	120T>C	Silent	
	464	464T>G	M155R	
	519	519C>T	Silent	
	668	668C>T	A223V	
	1059	1059T>C	Silent	
	1289	1289C>A	3'	
	1308	1308T>C	3'	
	1784	1784G>A	3'	

AF061655	AF061655	123920	GEN-LUJ	Cytidine deaminase, promoter [(SEQ ID NO:16)]
	575	575T>C	Intron	
	648	648T>C	Intron	
	771	771G>C	Intron	
	883	883G>A	Intron	
	941	941^insC	5'	
	1051	1051A>C	K27Q	

In the claims:

Claims 182-201 have been amended as follows:

182. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of [SEQ ID NO:15] SEQ ID NO:1 (methylenetetrahydrofolate reductase), the probe comprising at least one of:

(a) nucleotide 120 of SEQ ID NO:1 wherein T is replaced by C;

(b) [(a)] nucleotide 464 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by G;

(c) [(b)] nucleotide 519 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

(d) [(c)] nucleotide 668 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

(e) [(d)] nucleotide 1059 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C;

(f) [(e)] nucleotide 1289 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is is replaced by A;

(g) [(f)] nucleotide 1308 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C; and

(h) [(g)] nucleotide 1784 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] G is replaced by A;

or the complement thereof.

183. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of [SEQ ID NO:15] SEQ ID NO:1 (methylenetetrahydrofolate reductase), the probe comprising at least two of:

(a) nucleotide 120 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C;

(b) nucleotide 464 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by G;

(c) nucleotide 519 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

(d) nucleotide 668 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

(e) nucleotide 1059 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C;

(f) nucleotide 1289 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by A;

(g) nucleotide 1308 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C; and

(h) nucleotide 1784 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] G is replaced by A;

or the complement thereof.

184. The probe of claim 182 or 183 comprising no more than 500 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1.

185. The probe of claim 182 or 183 comprising no more than 200 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1.

186. The probe of claim 182 or 183 comprising no more than 100 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1.

187. The probe of claim 182 or 183 comprising no more than 50 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1

188. The probe of claim 182 or 183 comprising DNA.

189. The probe of claim 182 or 183 comprising a peptide nucleic acid.

190. The probe of claim 182 or 183 further comprising a detectable label.

191. The probe of claim 190 wherein the detectable label is a fluorescent label.

192. A method comprising:

(a) providing a test sample comprising nucleic acid molecules present in a biological sample obtained from an individual;

(b) contacting the test sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of [SEQ ID NO:15] SEQ ID NO:1, the probe comprising at least one of:

(i) nucleotide 120 of SEQ ID NO:1 wherein T is replaced by C;

[i] (ii) nucleotide 464 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by G;

[ii] (iii) nucleotide 519 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

[iii](iv) nucleotide 668 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

[iv] (v) nucleotide 1059 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C;

[v] (vi) nucleotide 1289 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by A;

[vi] (vii) nucleotide 1308 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C; and

[vii] (viii) nucleotide 1784 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] G is replaced by A;

or the complement thereof; and

(c) determining if the test sample comprises a nucleic acid molecule that hybridizes to the probe.

193. A method comprising:

(a) providing a test sample comprising nucleic acid molecules present in a biological sample obtained from an individual;

(b) contacting the test sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of [SEQ ID NO:15] SEQ ID NO:1, the probe comprising at least two of:

(i) nucleotide 120 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C;

(ii) nucleotide 464 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by G;

(iii) nucleotide 519 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

(iv) nucleotide 668 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by T;

(v) nucleotide 1059 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C;

(vi) nucleotide 1289 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] C is replaced by A;

(vii) nucleotide 1308 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] T is replaced by C; and

(viii) nucleotide 1784 of [SEQ ID NO:15] SEQ ID NO:1 wherein [N] G is replaced by A;

or the complement thereof; and

(c) determining if the test sample comprises a nucleic acid molecule that hybridizes to the probe.

194. The method of claim 192 or 193 wherein the probe comprises no more than 500 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1.

195. The method of claim 192 or 193 wherein the probe comprises no more than 200 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1.

196. The method of claim 192 or 193 wherein the probe comprises no more than 100 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1.

197. The method of claim 192 or 193 wherein the probe comprises no more than 50 contiguous nucleotides of [SEQ ID NO:15] SEQ ID NO:1.

198. The method of claim 192 or 193 wherein the probe is a DNA probe.

199. The method of claim 192 or 193 wherein the probe is a peptide nucleic acid probe.

200. The method of claim 192 or 193 wherein the probe comprises a detectable label.

201. The method of claim 200 wherein the detectable label is a fluorescent label.